56. The L1 protein of Claim 1, wherein said human papillomavirus ~~comprises~~ is either HPV-6 or HPV-11a.

57. The vaccine of Claim 12, wherein said human papillomavirus ~~compris-~~ ~~es~~ is either HPV-6 or HPV-11a.

58. The method of Claim 19, wherein the human papillomavirus ~~comprises~~ is either HPV-6 or HPV-11a.--

IN THE TITLE:

Delete the title and substitute therefor:

--Human Papillomavirus Vaccines Containing Conformationally Correct L1 Capsid Proteins--.

REMARKS

Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, the non-elected claims have been cancelled to expedite prosecution. Further, all of the claims are now restricted to human papillomavirus L1 proteins, compositions containing, and methods of use thereof. Also, Claims 50-55 are newly presented which are directed to vaccines and methods of use which consist essentially of recombinant conformationally correct human papillomavirus L1 proteins. Claims 56-58

respectively further limit the protein, vaccine and method of Claims 1, 12 and 19 by requiring that the human papillomavirus is either HPV-6 or HPV-11a. Upon entry of these claims, Claims 1-3, 10-26, 46-47 and 50-57 will be pending in this application. Further, Claims 1, 12 and 19 have been amended to obviate the outstanding § 112 issues. In particular, these claims all provide that the recombinantly expressed L1 protein or antigenic fragment thereof, reproduces the antigenicity and exhibits the same conformation as an L1 protein expressed on the surface of intact, native human papillomavirus virions. This claim language is intended to expedite prosecution on the merits and replaces the previous "capable of reproducing" language which the Examiner found to be objectionable. It is respectfully submitted that these amendments, along with the remarks and attachments to this Reply, should place this case in condition for allowance.

At the outset, Applicants would like to thank the Examiner for the courteous and helpful personal interview held with Examiner Caputa, Primary Examiner Sidberry, the inventors of this application, Bennett Jenson, Ph.D. and Richard Schlegel, Ph.D., M.D., and Applicants' undersigned representative. At this interview, all of the outstanding rejections were discussed in detail. The discussion during the interview is summarized below.

In particular, the § 112 second paragraph issues were discussed. The present amendments to Claims 1, 12 and 19 were specifically addressed. It was noted that the claims would likely be amended to recite that the L1 protein or antigen fragment reproduces the antigenicity and the conformation of an L1 protein expressed on the surface of native, intact papillomavirus virions. The Examiner indicated that this phraseology would likely obviate the § 112 second paragraph rejection.

The § 112 first paragraph and § 101 issues were addressed together at the interview since the issues are substantially the same. It was argued that the subject recombinantly produced L1 protein comprises at least one patentable utility which is not possessed by the virus *per se*, i.e., the protein is useful in the formulation of papillomavirus vaccines. It was noted that intact papillomavirus particles would be unsuitable for use as a vaccine because of their propensity to cause infection or transformation. Thus, it was argued that the recombinant L1 protein, by virtue of its method of production, exhibits a new utility not possessed by the virus.

It was also noted that the recombinant papillomavirus L1 proteins have utility for affinity purification of anti-L1 antibodies and for the preparation of antisera. Also, recombinant L1 proteins have utility in ELISA assays for measuring antibody titers in patients immunized against HPV, or in patients suspected of exhibiting HPV infection. It was further argued that the claimed utility, i.e., the use of L1 proteins to prevent papillomavirus infection, has been adequately demonstrated in the as-filed application and is further established by later submitted evidence, contained in the § 132 Declarations of record as well as in later published references relating to the use of conformationally correct papillomavirus L1 proteins as vaccines. Also, it is further noted that currently there is no known means for propagating HPV's in tissue culture. Thus, the virus could not feasibly be used for the isolation of HPV L1 proteins or for vaccine formulation.

It was further argued that the application adequately demonstrates that recombinantly produced L1 proteins produced according to the invention exhibit the same conformation and antigenicity as L1 proteins expressed on intact human papillomavirus virions. Specific reliance was made to the example in the specification which describes the

expression of HPV-1 L1 protein (in cos cells). It was argued that this recombinant protein conformationally and antigenically reproduces native HPV-1 L1 proteins based upon its reactivity with different monoclonal antibodies which specifically recognize conformational HPV-1 L1 epitopes.

Further, the data contained in the § 132 Declaration of Dr. Richard Schlegel was discussed. It was explained by the inventors that this additional data uses the COPV/-beagle dog animal model, which is the best available *in vivo* model for predicting efficacy of human papillomavirus vaccines. The similarities of COPV's and HPV's were discussed in great detail, i.e., similar L1 sequences, both at DNA and amino acid level, similar genetic organization, similar propensity to induce transformation, and similar mucosal route of infection. It was also noted that the COPV/beagle model allows for protective immunity to be evaluated using a natural site of infection rather than by more invasive methods of challenge, e.g., abrasion of tissue. The inventors noted that this is possible because the beagles studied comprise a beagle colony which exhibits a high incidence of oral wart formation as a consequence of papillomavirus infection.

The inventors also explained that the additional data contained in the Schlegel Declaration convincingly demonstrates that recombinant conformationally correct COPV L1 proteins protect naive weanling dogs against COPV challenge (100% of dogs immunized were protected) and also shows that this immunity may be passively transferred by administration of protective antisera obtained from naive weanling dogs which were inoculated with compositions containing conformationally correct COPV L1 proteins. It was also noted by the inventors that this additional data has subsequently been presented to other researchers (prominent in the papillomavirus area). Based on the similarities between COPV and

HPV's, this data was indicated to constitute the first convincing demonstration that compositions containing conformationally correct human papillomavirus L1 proteins may be used as vaccines for providing immunity against human papillomavirus infection. Also, these results provide the first demonstration that a systemically administered viral antigen formulation may be used to confer immunity against mucosal viral infection. This is contrary to previous research which had suggested that mucosal viral immunity required injection at a mucosal site of infection.

The § 112 rejection with respect to the use of antigenic fragments was also discussed. While it was acknowledged that proper conformation of the papillomavirus L1 protein is essential for a viable human papillomavirus vaccine, it was argued that one skilled in the art could, absent undue experimentation, express fragments of human papillomavirus L1 DNA's and ascertain whether the resultant L1 protein contains a sufficient number of conformational epitopes to afford protection upon challenge. It was also argued that this experimentation does not require that all the specific conformational epitopes be known and/or identified. This could be effected by expression of random human L1 DNA fragments in eukaryotic expression systems which provide for proper L1 protein conformation, e.g., the baculovirus expression system, cos cells, or other known and available eukaryotic expression systems.

Further, the scope rejection was discussed. While it was conceded that there exists sequence variation among L1 genes of different human papillomaviruses, it was noted (and supported by numerous literature references of record) that L1 genes, and human papillomavirus L1 genes in particular, are highly conserved in sequence, and that many L1 genes had been cloned and sequenced prior to the effective filing date of this application.

Thus, given this fact, one skilled in the art could, absent undue experimentation, practice the invention with other human L1 proteins other than those specifically exemplified and use other eukaryotic expression systems other than cos cells and baculovirus expression systems. In support of this traversal of the rejection, express reliance was made to later publications which describe the availability of other human L1 genes prior to the filing date of this application.

Finally, the prior art rejections were discussed. It was argued that none of the references teach or suggest a recombinant conformationally correct human L1 protein, or that such a protein could be used to provide immunity against human papillomavirus infection. For example, it was argued that the § 103 rejection based on Pilacinski et al. could not be sustained because this reference does not produce conformationally correct L1 proteins based on the *E. coli* expression system utilized. In fact, it was explained that the inventors used sera produced according to Pilacinski et al as a negative control to provide further evidence as to the essentiality of conformationally correct L1 proteins to a protective immune response. The inventors further noted that the L1 fusion proteins disclosed by Pilacinski et al (produced in *E. coli*), because they are not conformationally correct, do not protect cows against BPV infection. Moreover, the Pilacinski et al reference is further not relevant to the claims as amended because it does not relate to expression of a human papillomavirus L1 protein.

It was argued that it could not have been predicted from the art of record that human papillomavirus L1 proteins expressed in eukaryotic cells would be conformationally correct. For example, it was argued that the cited references which relate to expression of HPV-16 L1 protein, i.e., the Zhou et al. references, expressed an L1 sequence obtained

from an HPV-16 prototype which contains a site mutation which renders it assembly deficient and which upon expression does not result in a conformationally correct L1 protein. It was noted that this would be further discussed in the Reply to the Office Action and likely supported by a § 1.132 Declaration.

Turning now to the Office Action, the restriction requirement between Group I, Claims 1-3, 10-26, 46-47 and Group II, Claims 4-9, 41-45, and 48-49 is respectfully acknowledged. This requirement is rendered moot by cancellation of non-elected Claims 4-9, 41-45 and 48-49.

The title to the invention has been objected to as not being adequately descriptive. Accordingly, the title has been amended to read "Human Papillomavirus Vaccines Containing Conformationally Correct L1 Capsid Proteins." Withdrawal of this objection is respectfully solicited.

Claims 1-3, 10-26 and 46-47 stand rejected under 35 U.S.C. § 112, second paragraph. This rejection is respectfully traversed.

Claim 1 is stated to be indefinite in failing to provide proper antecedent basis for an L1 protein and to therefore be unclear. This rejection has been obviated by the amendment of Claim 1 to recite an L1 protein or antigenic fragment which <u>reproduces the antigenicity and exhibits the same conformation as an L1 capsid protein expressed on the surface of native, intact human papillomavirus virions</u>. The other independent claims have been similarly amended. These specific amendments were discussed at the personal interview with Examiner Caputa and he had indicated that they would obviate the rejection.

Claims 1, 12 and 19 have been amended to delete "capable of reproducing" and instead recite --reproduces--. Thus, it is clear that the antigenic fragment reproduces the

antigenicity of the L1 protein or antigenic fragment thereof. Therefore, based on the present amendments, withdrawal of the § 112 second paragraph rejection is respectfully requested.

Claims 1-3, 10-12 and 15-18 stand rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter. Essentially, the Examiner's position is that the claimed recombinant papillomavirus L1 proteins are unpatentable over the L1 protein expressed on the surface of papillomavirus virions, absent a new utility imparted by the method of preparation (recombinant expression) or purity.

This rejection is respectfully traversed. It is respectfully submitted that the subject recombinant human papillomavirus L1 proteins exhibit properties which are not inherent to the crude human papillomavirus virions. In particular, these proteins possess utility as vaccines for affording immunity in humans against papillomavirus infection. By contrast, the virus *per se* is unsuitable in this regard because, while it contains L1 proteins, it may produce undesirable side effects, e.g., administration may potentially give rise to infection and transformation which can result in condylomas, premalignant and malignant conditions.

Additionally, the recombinant human papillomavirus L1 protein has utility as an immunogen, i.e., it may be used to detect or affinity purify anti-L1 antibodies or it may be used to induce the production of anti-L1 antibodies. By contrast, the virus particles may give rise to different antibodies or react with other antibodies, e.g., antibodies to the L2 protein or other proteins which are also expressed by the particular papillomavirus. Also, as discussed *supra*, recombinant HPV L1 proteins have utility in ELISA assays for detecting HPV L1 antibody titers in human patients infected by human papillomavirus or immunized against human papillomavirus.

Thus, based on the foregoing, it is believed to be abundantly clear that recombinantly produced L1 proteins possess at least one patentable utility by virtue of their means of preparation and purity and therefore constitute statutory subject matter. Therefore, withdrawal of the § 101 rejection of Claims 1-3, 10-12 and 15-18 is respectfully requested.

Claims 15-26 also stand rejected under 35 U.S.C. § 101 as lacking patentable utility. Essentially, the basis of the rejection is that the specification and § 132 Declarations contain insufficient evidence that the claimed compositions and administration thereof to humans may be used to prevent papillomavirus infection. As noted *supra*, this rejection was also discussed in some detail at the interview. These specific arguments are reiterated and expanded upon. At the outset, it is noted that while the Examiner did not expressly indicate that he would vacate the rejection, he did state that he would likely favorably reconsider the rejection and likely withdraw the § 101 rejection, <u>if these same arguments were made on the record</u>.

In this regard, it is respectfully submitted that the as-filed application contains convincing evidence that recombinant human papillomavirus L1 proteins produced according to the invention are expressed in conformationally and antigenically correct form. This is established by the results in Example 2 relating to the expression of the HPV-1 L1 protein in cos cells. This example demonstrates that the resultant L1 expression product is full-length (55 KD), and reacts with murine monoclonal antibodies which are specific to conformational epitopes on the HPV-1 L1 protein. Moreover, it is further demonstrated that the resultant protein is intranuclearly localized, which is consistent with appropriate processing of the HPV-1 L1 protein.

During the interview the Examiner questioned whether the application contains data which would convince one skilled in the art that human papillomavirus L1 proteins have utility for affording immunity against human papillomavirus infection. More specifically, the Examiner questioned whether *in vitro* assays which relate to neutralization of BPV-1 are correlatable to human utility. The Examiner noted the dissimilarities between BPV and HPV's which cause human disease, e.g. the fact that HPV's, unlike BPV, cause cancer. The Examiner therefore took the position that BPV *in vitro* assays are not probative of the efficacy of human papillomavirus vaccines given the differences between the human and bovine papillomaviruses and further because the assays are *in vitro* rather than *in vivo*. Accordingly, applicants no longer rely on the *in vitro* assays relating to BPV-1 neutralization to establish utility of the claimed invention. Moreover, this basis of the rejection is believed to be moot based upon the additional data contained in the § 132 Declaration by Dr. Richard Schlegel. As explained by the inventors at the Examiner interview, this additional data in the COPV beagle animal model is believed to provide convincing *in vivo* evidence that recombinant conformationally correct human papillomavirus L1 proteins may be used as vaccines to prevent human papillomavirus infection because of the substantial similarities of COPV to HPV's. As was also explained by the present inventors, the COPV/beagle animal model is the best available animal model for predicting the efficacy of HPV vaccines in humans given the substantial similarities between COPV and HPV's which cause diseases in humans.

The extensive similarities of COPV and HPV's which cause disease in humans include, e.g., their similar L1 sequences (both at the DNA and protein level), the fact that both COPV and HPV's comprise mucosal papillomaviruses, the fact that both of these

viruses exhibit similar genetic organization, and the fact that both induce transformation. Given these similarities, it is reasonable to assume that the *in vivo* effects of COPV L1 proteins (immunoprotection upon challenge with infectious virus) and HPV L1 proteins will be similar.

In this regard, it is respectfully noted that the COPV data contained in the Schlegel Declaration shows that the administration of recombinant conformationally correct COPV L1 proteins provided 100% protection upon challenge. Further, this Declaration contains evidence that antisera obtained from immune weanling dogs immunized with said conformationally correct L1 proteins likewise induced passive protection (providing additional evidence that the immunity is indeed humoral).

As discussed *supra*, this animal model (which administers a COPV L1 protein expressed in a baculovirus expression system) is the best known available animal model for study of human papillomavirus vaccines. This fact is further established, e.g., by the Declaration by John Kreider, M.D. which accompanies this Reply. Therein, the Declarant, a well known expert in HPV research, notes that the COPV/beagle system is a suitable animal model for predicting the efficacy of human papillomavirus vaccines. Further, the Declarant states that in his opinion the experimental data contained in the Schlegel Declaration provides convincing evidence as to the efficacy of conformationally correct HPV L1 proteins as human papillomavirus vaccines. Moreover, his view is shared by other researchers. This data has been subsequently presented at several scientific meetings by the inventors and has been overwhelmingly lauded as constituting the first convincing demonstration that conformationally correct human papillomavirus L1 proteins may be used as

human papillomavirus vaccines, which constitutes the largest cause of human cervical carcinoma.

It is also respectfully noted that the grant proposal which culminated in the present invention was the most highly rated NIH grant proposal submitted in 1991, submitted in response to a request for animal models suitable for evaluating the efficacy of vaccines for affording immunity against human viral disease conditions. Moreover, the experts who reviewed this great proposal were specifically selected based on their expertise in human viral vaccines. Thus, experts in the area of viral vaccines regard this animal model to constitute the best animal model for predicting the potential efficacy of human viral vaccines. More specifically, the comments by the reviewers of this grant application (already of record) provide evidence as to the acknowledgement by those expert in human viral vaccines that the COPV/beagle model, given its similarities to HPV's which cause disease in humans, constitutes the best available *in vivo* model for study of human papillomavirus vaccines.

The Examiner has questioned the reliability of this data (in predicting human utility) on the basis that COPV L1 proteins could not be used to confer immunity against human papillomavirus infection (given the antigenic variation of L1 proteins expressed in different papillomavirus types and the type specificity of the immune response). However, this fact does not refute the efficacy of the claimed invention. It is acknowledged that COPV L1 proteins could, in all likelihood, not be administered to humans in order to confer immunity against HPV infection (given intrinsic type specificity of immune response and the antigenic variation of L1 proteins). However, this is respectfully believed to be irrelevant because: i) COPV is an acceptable *in vivo* model for HPV, ii) HPV L1 DNAs are known

and available, and iii) given the noted similarities of these viruses it is reasonable to expect that the results (protective immunity) may be extrapolated to HPV upon administration of HPV L1 proteins in humans as claimed herein. Thus, effective human papillomavirus vaccines for conferring immunity against a specific human papillomavirus will contain the corresponding conformationally correct HPV L1 protein.

It is further respectfully submitted that it is not necessary for establishing the utility of human papillomavirus vaccines that the specification identify the specific HPV L1 epitopes which induce the production of protective antisera. Quite clearly, this will vary dependent upon the particular human papillomavirus to which a vaccine is to be produced. This will, of course, determine which L1 protein is to be expressed and used in the formulation of a vaccine. However, there is no need that the particular epitopes be specifically identified because the application and § 132 Declaration demonstrates that conformationally correct papillomavirus L1 proteins (containing the requisite epitopes) may be produced which effectively neutralize the corresponding papillomavirus and afford protection upon *in vivo* challenge.

The § 101 rejection is further respectfully traversed based on the recently published proposed Utility Guidelines issued by the Patent Office. These guidelines expressly state that Examiners should not make utility rejections <u>if the claimed utility would be credible to those having ordinary skill in the art</u>. These new guidelines further state that Examiners are required to <u>accept utility statements made in the application or opinions of experts absent a rational reason to doubt the truth of such statements</u>.

Based on these proposed Utility Guidelines, maintaining the utility rejection would be totally improper based on the abundant evidence contained in the application and

the Declarations of record and those submitted with this Reply which demonstrate that the claimed utility is credible to those skilled in the art. In fact, a renowned papillomavirus expert, i.e., John Kreider, M.D., (as well as the present inventors), reviewed the COPV data and asserted that in his expert opinion the claimed utility relating to human papillomavirus vaccines, is credible. Moreover, the Examiner has presented no convincing evidence or reasoning to dispute the accuracy of this expert opinion.

It is respectfully submitted that based upon the above remarks, and those set forth at the interview, withdrawal of the § 101 rejection of Claims 15-26 is respectfully believed to be in order and is earnestly solicited.

Claims 1-3, 10-26, and 46-47 stand rejected under 35 U.S.C. § 112, first paragraph as not enabling the claimed invention. This rejection is based on essentially the same reasoning as the § 101 rejection. Accordingly, this rejection is respectfully traversed for the same reasons as the § 101 rejection which are incorporated by reference herein.

Moreover, the rejection is further traversed as it specifically pertains to the efficacy of human papillomavirus L1 antigenic fragments. It is respectfully submitted that based on the teachings in the application one could randomly express human papillomavirus L1 fragments, and identify those which are conformationally correct and therefore confer protection against the homologous papillomavirus (human papillomavirus which expresses the particular L1 protein). It is also respectfully submitted that this argument is <u>not</u> inconsistent with the traversal of the § 103 rejection. While it could not have been predicted from the references of record that human papillomavirus L1 proteins could be expressed in conformationally correct form, and used to confer protection against the homologous human papillomavirus, the subsequent demonstration of success (as evidenced by the results in the

application) will enable those skilled in the art to extrapolate the invention to the expression of conformationally correct L1 fragments containing less than an entire human papillomavirus L1 sequence. It is further conceded that not all L1 fragments will not be efficacious. Also, it is further acknowledged that the particular expressed L1 DNA sequence will be significant as to whether a conformationally correct L1 protein is obtained (as evidenced by the fact that a mutation at a single site in the HPV-16 L1 gene gives rise to an assembly deficient mutant and non-conformational L1 proteins). However, notwithstanding this fact, it is still reasonable to expect, based on the teachings of the application, that HPV L1 fragments which reproduce the antigenicity and conformation of the L1 protein expressed on the surface of human papillomavirus virions may be obtained according to the disclosed methods and used in the formulation of human papillomavirus vaccines. Moreover, while it is acknowledged that the specific sequence of efficacious L1 fragments cannot be predicted *a priori*, this is irrelevant because efficacious fragments may be identified according to the disclosure and known assays. This would entail, e.g., ascertaining those L1 fragments which upon expression bind to antibodies which are specific to conformational epitopes contained in the particular expressed human papillomavirus L1 protein, such as is described with respect to the exemplified recombinant HPV-1 L1 protein.

The claims are also rejected for failing to enable expression and use of L1 proteins as papillomavirus vaccines as is generically claimed. This rejection is respectfully traversed to the extent it may be applicable to the claims as amended, which are restricted to human papillomavirus L1 proteins.

As discussed at the interview, the as-filed application, and the declarations of record provide adequate evidence that the subject recombinant human papillomavirus L1

proteins, which conformationally and antigenically reproduce L1 proteins on native human papillomavirus virions, may be used as an immunogen to protect against the homologous papillomavirus (defined as previously). This has been shown based on the subject application which exemplifies expression of the HPV-1 L1 protein (and shows that the expressed L1 protein is conformationally and antigenically correct) and based upon the data contained in the Schlegel Declaration relating to the COPV beagle animal model which demonstrates that the administration of conformationally correct COPV proteins to beagle dogs results in total protection (which constitutes the best available animal model for study of HPV).

Moreover, while the disclosure concededly only exemplifies recombinant expression of a specific HPV-L1 protein, i.e., HPV-1 L1 protein, based on the fact that many other human L1 genes had been previously cloned and sequenced (See, e.g., Baker, Carl, "Sequence Analysis of Papillomavirus Genes," 321-384, 1987 of record herein), it would not rise to the level of undue experimentation based on the teachings in this application to express other human papillomavirus L1 proteins in conformationally correct form, and use same in the formulation of HPV vaccines. Also, the fact that conformationally correct L1 proteins have been expressed in very dissimilar eukaryotic expression systems, i.e., cos cells and insect cells, is believed to provide further evidence that the claims should not be restricted to human papillomavirus L1 proteins expressed in cos cells. While it is conceded that success could not have been predicted at the outset (given the inherent unpredictability associated with the expression and assembly of recombinant viral capsid proteins in conformationally correct form), the requisite predictability has subsequently been demonstrated based on the fact that positive results, i.e., the expression of conformationally correct papillomavirus L1 proteins, have been obtained in different expression systems.

Therefore, based on the foregoing and in light of the present amendments, withdrawal of the § 112, first paragraph, rejection of Claims 1-3, 10-26 and 46-47 is further respectfully believed to be in order and is earnestly solicited.

Turning now to the art rejections, Claims 1-3, 10-26, and 46-47 stand rejected under 35 U.S.C. § 103 as being unpatentable over Pilacinski et al., and further in view of Sambrook et al., Danos et al. (U.S. Patent No. 4,551,270), Schwarz et al., Cole et al. (1986), Seedorf et al., Baker et al., Cole et al. (1987) and Danos et al. (EMBO. Journal 1982). This rejection is respectfully traversed.

Essentially, the basis of the rejection is that Pilacinski et al. discloses the expression of BPV L1 fusion proteins in *E. coli*, and Danos et al. disclose use of L1 peptides coupled to an immunogenic carrier. The Examiner further asserts that it would have been obvious to have expressed L1 sequences in eukaryotic cells to obtain conformationally correct L1 proteins based on Sambrook et al. who teach that a known disadvantage associated with bacterial expression systems is that they may give rise to improperly folded proteins and that this problem may be alleviated by the use of eukaryotic cells such as cos and insect cells. Further, the expression of the specifically recited human papillomavirus L1 sequences is asserted to have been obvious based on the secondary references, i.e., Schwarz et al., Cole et al. (1986), Seedorf et al., Baker et al., Danos et al. (U.S. Patent No. 4,551,270) and Cole et al. (1987). This rejection is respectfully traversed.

At the outset, it is respectfully noted that Pilacinski et al. is not suggestive of the claimed invention because it is restricted to the expression of BPV-1 L1 proteins and use thereof. By contrast, the present claims are restricted to human papillomavirus L1 proteins and the use thereof as vaccines.

Moreover, as discussed at the interview, and as recognized by the Examiner, Pilacinski et al. is further not suggestive of the claimed invention because they do not teach the production of conformationally correct papillomavirus L1 proteins or fragments which reproduce the antigenicity and conformation of L1 proteins expressed on the surface of papillomavirus virions as claimed herein. Rather, Pilacinski et al. express BPV-L1 and L2 fusion proteins which are not conformationally correct and which moreover do not reproduce the antigenicity of the native BPV-L1 protein. This is clear, e.g., based on the disclosure of page 359, right hand column wherein Pilacinski et al. notes that "[a]ntigen raised against the large ß-gal fusion proteins reacted 10 to 100-fold more weakly than antisera against whole, purified BPV-1." Also, the reference further notes that their results suggest "that a great majority of the BPV-1 antigenic sites were not presented to the immune system."

In fact, as discussed *supra*, the present inventors utilized antisera produced according to Pilacinski et al as a negative control specifically based on the fact that it was not produced against conformationally correct papillomavirus L1 proteins and therefore does not provide for immunity against BPV-1 viral in cows. To the contrary, the antisera of Pilacinski et al, because it was produced against non-conformational L1 proteins, expressed in *E. coli* (specifically lineaer BPV-1-B-galactosidase fusion proteins) predominantly results in antibodies which are specific for linear L1 epitopes.

The fact that the present inventors used the sera of Pilacinski et al as a negative control may be appreciated by review of the application at page 21, line 18 to page 22, line 4. It is clear therefrom that the inventors administered to cows antigen formulations produced according to Pilacinski et al containing BPV-L1-B-galactosidase fusion proteins. However, while 90% and 58% of the cows developed antibody responses to internal and

external BPV-1 epitopes, all the cows still developed fibromas. Thus, it is clear from the present disclosure that antigens produced according to Pilacinski et al are not conformationally correct and therefore fail to confer protection.

Also, as noted, Pilacinski et al. is further remote to the present claims because it is limited to expression of BPV-1 L1 proteins. By contrast, the present claims are now restricted to human papillomavirus L1 proteins, compositions containing and methods of use thereof.

The Examiner took the position that it would have been obvious to have instead expressed human papillomavirus L1 sequences in eukaryotic cells using eukaryotic expression vectors (instead of bacterial cells) based on Sambrook with the expectation that the protein would reproduce the antigenicity and conformation of the native human papillomavirus L1 protein. However, this is respectfully traversed.

While it might have been obvious to try to express human papillomavirus L1 sequences in eukaryotic cells in order to obtain conformationally, antigenically intact L1 proteins, this is not the proper standard of obviousness. In re Mercier, 185 USPQ 774 (CCPA 1975); In re Antonie, 195 USPQ 6 (CCPA 1977). Moreover, contrary to the Office Action, the successful outcome (conformationally correct L1 proteins which reproduce the antigenicity of native human papillomavirus L1 proteins and which are suitable for usage in the formulation of human papillomavirus vaccines) was not expected. To the contrary, there is a high level of unpredictability associated with producing recombinant viral proteins in conformationally correct form. Also, there is a high level of unpredictability associated with the design of effective viral vaccines. Therefore, while the selection of eukaryotic cells for

expressing L1 capsid proteins of might have been obvious to try, it was entirely possible that such methods would have been totally unsuccessful.

For example, it was possible that the human papillomavirus L1 protein would need to be expressed on the surface of an intact papillomavirus for proper conformation to be obtained. Alternatively, the L2 capsid protein or other papillomavirus proteins, e.g., E4, or other papillomavirus DNA's, could have been necessary to provide for proper assembly and production of a conformationally correct L1 protein. Thus, it could not have been predicted absent Applicants' disclosure that human papillomavirus L1 DNA upon expression in the absence of other papillomavirus proteins or DNAs would give rise to conformationally correct L1 proteins. This argument is supported both by literature references relating to expression of papillomavirus capsid protein sequences as well as to other references relating to the recombinant expression of other viral capsid proteins. For example, it is noted that the human B19 parvovirus requires both VP1 and VP2 capsid protein expression to obtain proper assembly and the induction of neutralizing antibodies. (Kajigaya et al., Proc Natl Acad Sci, USA, 88, 4646-4650 (1991)). Also, bluetongue virus and polyomavirus similarly require the expression of two distinct capsid proteins for the assembly of virus-like particles. (Louden et al, Virology, 182, 793-801 (1991); Salonke et al, Cell, 46, 895-904 (1986)). Moreover, earlier research had similarly suggested that the expression of both of the human papillomavirus L1 and L2 proteins was necessary for proper assembly of HVP virus-like particles and proper conformation (Zhou et al., J. Virol., 185, 251-257, (1991)). However, surprisingly this has been found not to be the case for human papillomaviruses. Rather, the present inventors have discovered that L1 expression alone is sufficient for the production of conformationally correct HPV L1 proteins.

Still alternatively, it was possible that proper conformation could have required expression in specific eukaryotic cells, e.g., due to glycosylation or because of inherent fastidiousness of papillomaviruses and the cells which they infect. Therefore, it was possible that proper conformation could only be obtained in cells which the particular HPV virus normally infects or which glycosylate the protein in a certain way.

However, unexpectedly it has been discovered by the present inventors that L1 human papillomavirus sequences, when expressed in the absence of other papillomavirus sequences, result in L1 proteins which reproduce the antigenicity and conformation of L1 proteins on native papillomaviruses. This outcome was not expected, and in fact was contrary to prior research (Zhou et al., Id. (1991)).

It is further respectfully submitted that the addition of the secondary references does not remedy the deficiencies of the rejection. While these references provide evidence that many L1 sequences, including human papillomavirus L1 sequences, had been known and available and had been fused to immunogenic carriers, these references do not provide any reasonable expectation that these sequences, if expressed in eukaryotic cells, in the absence of other HPV sequences, would have resulted in L1 proteins which reproduce the antigenicity and conformation of L1 proteins expressed on the surface of cells infected by native human papillomavirus virions and provide protection against papillomavirus infection.

It should further be emphasized that these arguments do not refute the enablement of the generic claims. While the outcome could not have been expected prior to the present invention, once it had been established that human papillomavirus L1 DNAs may be expressed in eukaryotic systems to produce conformationally correct human papillomavirus L1 proteins which reproduce the antigenicity of native L1 proteins, it is reasonable to

assume that this result may be extrapolated to other eukaryotic expression systems and with other human papillomavirus L1 sequences.

Also, it could not have been predicted from the cited references that the L1 proteins would function as a viable vaccine for affording immunity against human papillomavirus infection. Prior to the subject disclosure, it had not been known that a human papillomavirus L1 protein could be used to protect humans against papillomavirus infection. This is evidenced, e.g., by the excerpt from "Papillomaviruses and Human Cancer," pp. 238-251, Herbert Pfister, editor, CRC Press, which is attached to this Reply. Kindly note that in the section relating to prophylaxis at page 247 the author notes that "there is presently no evidence for a possible prevention of HPV infection by the use of a capsid protein." Thus, this recent review article provides evidence that experts in the field did not regard the use of human papillomavirus L1 proteins as vaccines to be obvious.
Moreover, while all the claims are believed to be patentable, the patentability of newly submitted Claims 50-55 is separately argued. These claims are directed to compositions and methods of use which consist essentially of papillomavirus L1 proteins. Thus, these claims exclude the presence of additional moieties, e.g., proteins, which affect the essential properties of the composition, e.g., other antigens such as the L2 capsid protein.

With respect to the separate patentability of these claims, the Declaration of Joanne Suzich contains evidence that L1 proteins, by themselves, i.e., in the absence of L2 proteins, provide for substantially better immunoprotection than virus-like particles containing a combination of L1 and L2 proteins. This is demonstrated by the results summarized in the Table of this Declaration.

Quite clearly, this result could not have been predicted from the references of record. In fact, the results are contrary to the Zhou reference (Zhou et al., Virology, 185(1), 251-257, 1991), which taught that both L1 and L2 are necessary for production of virus-like particles.

The reasonable expectation would have been that the presence of both L1 and L2 would have been preferred to L1 alone, since this would likely produce virus-like particles which more closely mimic the antigenicity of the HPV virus, essentially because the HPV virus normally expresses both L1 and L2 capsid proteins. Therefore, it would have been reasonable to assume that both proteins would be required for assembly of virus-like particles (as Zhou et al. (1991) erroneously disclosed), and further that both proteins may contain epitopes involved in humoral immunity.

However, the results contained in the Declaration, which compares the *in vivo* effects of COPV L1 and L2 containing virus-like particles and COPV L1 virus-like particles (expressed in a baculovirus system) indicate that the L1 particles provided greater protection in canines than did particles comprised of L1 and L2 proteins. In view of this result, which was totally unexpected and contrary to Zhou et al. (1991), Claims 50-55 should at the least be found patentable.

Withdrawal of the § 103 rejection of Claims 1-3, 10-26 and 46-47 based on Pilacinski et al., in view of Sambrook et al., Danos et al. (U.S. Patent No. 4,551,270), Schwarz et al., Cole et al. (1986), Seedorf et al., Baker et al., Cole et al. (1987) and Danos et al. (EMBO. Journal 1982) is therefore respectfully requested.

Claims 1-3, 10-12, 15-18, and 46-47 stand rejected under 35 U.S.C. § 103 as being unpatentable over Zhou et al. (J. Virol.. 185, 251-257 (1991)). This rejection is respectfully traversed.

Zhou et al. describes expression of prototype HPV-16 L1 and L2 open reading frames in epithelial cells. The reference further describes at page 255, that expression of HPV-16 L1 and L2 genes in epithelial cells is both necessary and sufficient to allow assembly of virion-like particles.

However, contrary to the present invention, Zhou et al. do not produce conformationally correct human papillomavirus L1 proteins as are claimed in the present invention. This is notwithstanding the fact that Zhou et al. teach expression of an HPV-16 L1 sequence in a eukaryotic expression system. Rather, Zhou et al. obtain expression of non-conformational HPV-16 L1 proteins which would therefore be unsuitable for use as a protective immunogen.

As explained at the interview, and as supported by Roden et al., J. Virol., 68, 7260-7266, (1994) and the § 132 Declaration by A. Bennett Jenson submitted herewith, Zhou et al. express a prototype HPV-16 L1 sequence. This is clear based on the fact that they disclose as the source of their HPV-16 L1 DNA, Dr. Gissman, a collaborator of Dürst et al. This prototype L1 sequence is derived from an HPV-16 genome which integrated into the chromosomes of cervical squamous cell carcinoma and which was originally reported by Dürst et al., Proc. Natl. Acad. Sci., USA, 80, 3812-15, (1983).

This prototype HPV-16 differs from the wild-type HPV-16 in the fact that it contains a point mutation which changes an aspartic acid residue at position 202 to a histidine. This single modification, moreover, has substantial effects.

For example, it results in the production of capsid proteins which do not exhibit the normal icosahedral structure of HPV-16 particles. Electron microscopic comparison of the prototype HPV-16 particles shows that the prototype HPV-16 L1 proteins produce heterogeneous particles 35-40 nm in diameter with no evidence of icosahedral symmetry (Kirnbauer et al., J. Virol., 67, 6429-6436 (1993)). By contrast, wild-type HPV-16 particles are homogeneous and symmetrical, i.e., exhibit icosahedral symmetry and comprise identical diameters of about 50 nm. Also, as discussed in Roden et al. (Id.), the HPV-16 L1 modification results in a defective assembly mutant. Roden et al. indicate that this single point mutation makes the HPV-16 assembly three orders of magnitude less efficiently than the wild-type HPV-16.

Further, and more importantly, particles obtained by expression of the HPV-16 L1 sequence do not result in particles suitable for use as a vaccine. This is evidenced, e.g., by the last page Roden et al. wherein the authors note that antisera raised to particles obtained by expression of the HPV-16 prototype failed to prevent binding of wild-type HPV-16 virus-like particles to cell surfaces.

This provides strong evidence that the HPV-16 prototypes does not result in an effective immunogen, i.e., one which induces the production of protective antisera. In fact, Roden et al. conclude based on their results that wild-type HPV-16 particles would be a "more attractive candidate" for a human papillomavirus vaccine. The fact that the HPV-16 prototype L1 sequence does not result in conformationally correct human papillomavirus L1 proteins, i.e., L1 proteins which reproduce the antigenicity and conformation of L1 proteins expressed on the surface of native, intact HPV-16 virions is further established by the Jenson Declaration submitted herewith.

This Declaration describes an immunofluorescence assay wherein the prototype HPV-16 L1 sequence and the wild-type L1 sequence were both expressed in Sf9 insect cells (using a baculovirus expression system) and tested for their reactivity with monoclonal antibodies. More specifically, the ability of the resultant L1 proteins to bind to six conformational antibodies, i.e., antibodies specific to HPV-16 conformational epitopes and one antibody specific for a linear epitope was compared by immunofluorescence.

These results demonstrated that all of the seven monoclonal antibodies bound to the cells which expressed wild-type HPV-16 L1 particles. By contrast, cells which expressed the prototype HPV-16 particles failed to react with any of the six tested conformational antibodies. Moreover, this was despite the fact that the prototype HPV-16 L1 is synthesized, transported into the nucleus and aggregated in a manner similar to the wild-type HPV-16 L1 proteins as shown by its reactivity with an antibody specific to a linear non-conformational HPV-16 L1 epitope. Thus, while the prototype HPV-16 L1 protein aggregates similar to the wild-type HPV-16, L1 protein, it still fails to react with antibodies which recognize conformational HPV-16 L1 epitopes. Thus, this Declaration is believed to contain convincing evidence that expression of the HPV-16 prototype, as disclosed by Zhou et al., does not produce conformationally correct L1 proteins as claimed herein. Moreover, based on the failure of the prototype HPV-16 L1 proteins to inhibit binding of the wild-type HPV-16 to cell surfaces, it is further clear that Zhou et al. fail to describe an immunogen which would be suitable for use as a vaccine.

It is also noted that experiments were attempted by the Declarant to compare the ultrastructure of the prototype HPV-16 to wild-type HPV-16 virus-like particles by electron microscopy. However, such a comparison was not possible because of the inability

to assemble the prototype HPV-16 L1. This is consistent with the lack of proper conformation of the prototype HPV-16 L1 particles, and further with Zhou et al., who disclose that both HPV-16 L1 and L2 expression in epithelial cells is necessary for assembly of virion-like particles. (See, page 255 of Zhou et al., Virology, 185, 251-257, (1991)). Thus, based on these results, it is quite clear that Zhou et al. failed to produce HPV-16 L1 proteins which reproduce the antigenicity and conformation of a L1 protein expressed by wild-type, intact papillomavirus virions as claimed herein.

Also, while all of the claims are believed to be patentable over Zhou et al., newly introduced Claims 50-55 are believed to be separately patentable over Zhou et al. These claims are directed to a composition consisting essentially of conformationally correct L1 proteins and the use thereof as a vaccine for affording immunity against human papillomavirus infection. Quite clearly Zhou et al. does not teach such a composition or a method, and in fact teaches away from the use of L1 protein by itself as an immunogen.

As discussed *supra*, Zhou et al. erroneously disclosed (because they expressed prototype HPV-16 L1 sequence) that both L1 and L2 proteins are necessary for assembly of virus-like particles possessing the requisite immunogenicity. For example, at page 255, the authors state "expression of HPV-16 L1 and L2 genes in epithelial cells is both necessary and sufficient to allow assembly of virion-like particles."

Thus, Zhou et al. would clearly teach against the use of papillomavirus L1 proteins, by themselves, as a vaccine against papillomavirus infection. Moreover, the non-obvious use of papillomavirus L1 capsid proteins as a vaccine is further evidenced by a recent review article relating to potential papillomavirus therapeutics by Herbert Pfister. Therein, the author expressly states that "there is presently no evidence for a possible

prevention of HPV infection by use of a capsid protein." (See, Herbert Pfister, "Papilloma-viruses and Human Cancer", pp. 238-251, Herbert Pfister, editor, CRC Press, at page 247, attached to this Reply). It should be noted that this review article was published prior to public disclosure of the results obtained by the present inventors.

Further evidence as to the non-obviousness of Claims 50-55 may be found in the § 132 Declaration of Joanne Suzich attached to this Reply. This Declaration describes an experiment which compares the level of protection afforded by recombinant COPV L1 particles to particles comprising a mixture of COPV L1 and L2 virus-like particles. As discussed *supra*, these results surprisingly indicated that L1 particles achieved better protection than did a mixture of L1 and L2 particles. Quite clearly, these results could not have been predicted from Zhou et al. (1991), who erroneously disclosed that both L1 and L2 are necessary for the assembly of immunogenic human papillomavirus virus-like particles.

Therefore, based on the foregoing, withdrawal of the § 103 rejection of Claims 1-3, 10-12, 18, 46 and 47 based in Zhou et al. (1991) is respectfully believed to be in order and is earnestly solicited.

Claims 1-3, 10-11 and 46-47 stand rejected under 35 U.S.C. § 102(b) as anticipated by, or in the alternative as obvious over Zhou et al., J. Gen. Virology, 71, 2185-2190, (1990).

This reference, as with the previously described Zhou et al. (1991) reference, relates to expression of the prototype HPV-16 L1 protein. This prototype is expressed in a recombinant vaccinia virus which lacks serine protease inhibitor genes. The fact that Zhou et al. use the HPV-16 prototype may be discerned based on their source of the HPV-16 DNA fragment. In particular, this DNA was obtained from HPV-16-pAT153 (Dürst et al.,

Proc. Natl. Acad. Sci., USA, 80, 3812-3815, (1983)) which is the same prototype HPV-16 L1 sequence expressed by Zhou et al. in their subsequent 1991 paper.

Therefore, the same arguments set forth *supra* with respect to Zhou et al. (1991) are equally germane to Zhou et al. (1990). Essentially, because Zhou et al. express the prototype HPV-16 L1 gene, they could not have obtained conformationally correct L1 proteins which reproduce the antigenicity of native L1 proteins as claimed herein. This is notwithstanding the fact that the prototype L1 protein provides for the assembly (although substantially less efficiently) of virus-like particles (of smaller diameter than wild-type HPV-16 virus-like particles), which are transported to the nucleus like wild-type L1 protein (as established by the reaction of the prototype HPV-16 L1 protein with an HPV-16 L1 antibody which is specific to a non-conformational HPV-16 L1 linear epitope). The fact that the prototype HPV-16 L1 sequence does not result in conformationally correct L1 proteins is established by the Roden et al. paper as well as the § 132 Declaration of A. Bennett Jenson which are discussed *supra*. Moreover, this fact is further implied by Zhou et al. (1991) Id. which describes that expression of the HPV-16 prototype L1 protein by itself does not provide for proper assembly. By contrast, efficient L1 assembly and the production of conformationally correct HPV-16 L1 proteins is obtained in the absence of the L2 protein if the wild-type HPV-16 is expressed rather than the prototype.

Thus, Zhou et al. (1990), fails to teach or suggest an L1 protein which would be suitable for use as a vaccine. To the contrary, because of its lack of proper L1 conformation, the L1 expressing recombinant vaccinia of Zhou et al. would not be suitable for use as a vaccine.

This is supported by the later Zhou et al. (1991) paper, which suggests that antisera produced against the HPV-16 prototype would not confer protection against HPV-16, based on the fact that it does not inhibit binding of the wild-type HPV-16 to cell surfaces.

Therefore, based on the foregoing, withdrawal of the § 102 and § 103 rejection of Claims 1-3, 10-11 and 46-47 based on Zhou et al. (1990) is respectfully believed to be in order and is earnestly solicited.

Claims 1-3, 12, 19, 46-47 also stand rejected under 35 U.S.C. § 102(a) as anticipated by, or in the alternative as being obvious over Lin et al., Virology, 187(2), 612-619 (1992).

As properly described by the Examiner, this reference relates to the expression of cottontail rabbit papillomavirus L1 protein (CRPV) using a vaccinia vector in BHK cells. This reference is removed as an anticipatory reference based on the present amendment which limits all of the pending claims to human papillomavirus L1 proteins, compositions containing, and methods of use thereof.

Claims 13-14, 16-17, 19-26 stand rejected under 35 U.S.C. § 103 as being unpatentable over Zhou et al. (J. Virology, 185, 251-257 (1991)), further in view of Danos et al. (U.S. Patent No. 4,551,270), Schwarz et al., Cole et al. (1986), Seedorf et al., Baker et al., Cole et al. (1987) and Danos et al (EMBO. Journal 1982).

This rejection is respectfully traversed for essentially the same reasons set forth *supra* in the traversal of the § 103 rejection of Claims 1-3, 10-12, 15, 18 and 46-47 based on Zhou et al. (1991) which are incorporated by reference herein.

The addition of the secondary references do not compensate for the deficiencies of the Zhou et al. reference. While these references concededly provide evidence that many human papillomavirus L1 genes had previously been cloned and sequenced (prior to the filing date of this application), they provide no motivation to use such L1 proteins as a vaccine for affording immunity against human papillomavirus infection as claimed.

Also, the non-obviousness of the invention is further supported by Pfister et al., discussed *supra*. Moreover, with respect to Claims 50-55, it further could not have been predicted from those references that the administration of L1 proteins, in the absence of other immunogens, e.g., L2, would provide an effective vaccine for affording immunity to papillomavirus infection.

Therefore, in view of the above remarks, rejection of Claims 13-14, 16-17 and 19-26 based on Zhou et al. (1991) taken in view of Danos et al. (U.S. Patent No. 4,551,270), Schwarz et al., Cole et al. (1986), Seedorf et al., Baker et al., Cole et al. (1987) and Danos et al. (EMBO. Journal 1982), is respectfully solicited.

Claims 12-26 stand rejected under 35 U.S.C. § 103 as being unpatentable over Zhou et al. (1990) taken in view of Danos et al. (U.S. Patent No. 4,551,270), Schwarz et al., Cole et al. (1986), Seedorf et al., Baker et al., Cole et al. (1987) and Danos et al. (EMBO. Journal 1982).

This rejection is respectfully traversed for the reasons set forth in the traversal of the rejection of Claims 1-3, 10-11, and 46-47. These arguments are incorporated by reference herein.

Essentially, Zhou et al. fails to describe conformationally correct L1 proteins which could be used as a papillomavirus vaccine, and further fails to suggest the use of L1

proteins as a vaccine against papillomavirus infection. The mere fact that Zhou et al. observed an enhanced antibody response (by incorporation of the L1 gene in vaccinia) is irrelevant absent any indication that the resulting antibodies confer immunoprotection. Also, as discussed *supra*, it has been established that Zhou et al. does not obtain conformationally correct L1 proteins suitable for use as a vaccine, based on the fact that they express the HPV-16 prototype and not the wild-type HPV-16 L1 DNA.

The addition of the secondary references does not compensate for the deficiencies of the primary reference. These references cumulatively establish that many human papillomavirus L1 genes had been cloned and sequenced prior to the filing date of this application. This is conceded. In fact, many of the cited references are incorporated by reference in the application. However, this is irrelevant absent any suggestion in these secondary references which would indicate that such L1 proteins could be used to confer immunity against human papillomavirus infection.

Also, Zhou et al. fails to disclose the preparation of L1 proteins which could be used as a vaccine against papillomavirus infection. As discussed *supra*, subsequent research has demonstrated (as shown in Roden et al. and the § 132 Declaration of A. Bennett Jenson) that the L1 proteins of Zhou et al. are not conformationally correct and are therefore totally unsuitable as a vaccine. Moreover, the non-obviousness of the claimed invention is further supported by Pfister et al. who disclose that capsid proteins could not be used to confer protection against HPV infection.

Therefore, based on the foregoing, withdrawal of the § 103 rejection of Claims 12-26 based on Zhou et al. (1990) taken in view of Danos et al. (U.S. Patent No.

4,551,270), Schwarz et al., Cole et al. (1986), Seedorf et al., Baker et al., Cole et al. (1987) and Danos et al. (EMBO. Journal 1982), is respectfully requested.

The § 103 rejection of Claims 13-18 and 20-26 based on Lin et al. taken in view of Danos et al. (U.S. Patent No. 4,551,270), Schwarz et al., Cole et al. (1986), Seedorf et al., Baker et al., Cole et al. (1987) and Danos et al. (EMBO. Journal 1982), is also respectfully traversed. Applicants further expressly reserve the right to remove this reference (two months prior to the subject filing date) by the submission of a § 131 Declaration.

As argued *supra*, Lin et al. fails to teach or suggest the claimed invention which is limited to human papillomavirus L1 proteins, vaccines containing, and methods of use thereof. To the contrary, this reference is restricted to the expression of rabbit cottontail papillomavirus L1 proteins, and their administration in rabbits to confer immunity. Thus, this reference is not germane to the claims as amended.

Moreover, the secondary references do not remedy the deficiencies of Lin et al. While they cumulatively establish that many human papillomavirus L1 genes had been cloned and sequenced, none of these references provides any indication that the resultant expression products could be used to confer immunity against human papillomavirus infection.

Therefore, withdrawal of the § 103 rejection of Claims 13-18 and 20-26 based on Lin et al. taken in view of Danos et al. (U.S. Patent No. 4,551,270), Schwarz et al., Cole et al. (1986), Seedorf et al., Baker et al., Cole et al (1987) and Danos et al. (EMBO. Journal 1982), is respectfully requested. It is moreover believed that this case is in condition for allowance.

However, if any issues remain outstanding, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

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